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Osteomyelitis in complicated bones- the role of FDG PET/CT

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Abstract

Osteomyelitis in infections encompasses heterogeneous group of condition that frequently have high morbidity and a come at a huge cost to healthcare system. Accurate and early diagnosis is important for the proper management of the condition. FDG PET/CT has been found useful in the osteomyelitis of complicated bones, including prosthetic joint infections, fracture related infections and sternal wound infections. The altered anatomy and the replacement of marrow in some cases of metallic implant makes the use of anatomic-based methods less optimal. FDG PET/CT has been found to be useful under these circumstances, however, it also has its own limitation of lack of specificity especially due to inflammation. Recent meta-analysis of the role of FDG PET/CT in complicated osteomyelitis have result in the validation defined the indications for its use. This has led to the publication of best use criteria and recommendations of by joint committees of major nuclear medicine societies.

Key words: FDG PET/CT; fracture related infections; sternal osteomyelitis; infected joint prosthesis; osteomyelitis; metanalysis

Introduction

Osteomyelitis, an infection of the bone and marrow, is a devastating disease that needs prompt and early diagnosis, therapeutic interventions including prolonged antibiotic therapy and other surgical interventions.¹ Osteomyelitis is a heterogeneous condition which can affect any bone in the body under different medical conditions. Infection to the bone may occur through hematogenous spread from another site of infection, or inoculation of infection from contamination of an open fracture or from the microflora of the patient's skin during surgical interventions. Lastly osteomyelitis can spread from infected adjacent soft tissue such as in patients with diabetes mellitus with infected diabetic foot ulcers, the infection spreads to the underlying bone. Osteomyelitis of complicated bone poses a significant challenge in its management and the overall burden to healthcare systems globally, the healthcare personnel involved in the treatment of osteomyelitis and the patient suffering from it². The management of complicated osteomyelitis is much higher than simple osteomyelitis usually requiring multiple surgical revisions, complex antibiotic regimens and a multidisciplinary clinical

approach involving a co-ordinated effort from many disciplines including the orthopaedic or trauma surgeon, the microbiologist, medical imaging specialist, specialist nursing care, physiotherapist in some cases input from a vascular surgeon, endocrinologist and other specialist may be needed.³

Pathogens of osteomyelitis

In osteomyelitis, the infection may be caused by bacteria, viruses, fungi or pathogens. Bacteria are the most common cause of osteomyelitis. Of the bacteria, *Staphylococcal sp.* is the most common bacterial cause of osteomyelitis with *Staphylococcus aureus* the most common of that species including methicillin resistant strains.⁴ *Streptococcus epidermidis* a skin contaminant is frequently involved when there is contamination from the skin. In recent years, polymicrobial bacteria including gram negative bacteria have been identified in some cases.⁵ Some bacteria have important therapeutic implications as they may be drug-resistant. In other bacteria like the *Staphylococcus sp.*, the bacteria form biofilms on the surface of prosthetic implant or nonviable bone surface that allow them to evade the immune system, prevent antibiotics from reaching the bacteria.^{6,7} The bacteria may alter their virulence and survive in neutrophils macrophages and even osteoclast. This allows them to remain viable and lead to prolonged chronic osteomyelitis. Sometimes osteomyelitis may be due to relatively less common organisms such as fungal infections such as *Candida sp.* or *Mycobacteria sp.* amongst others⁸. These organisms pose a significant problem in their management because their diagnosis can be challenging, and the management may require very long period of antimicrobial for very long periods which have significant adverse events and in many cases the duration of antimicrobial therapy may not be well defined.⁹

Osteomyelitis in complicated bone

Uncomplicated osteomyelitis is usually due to hematogenous spread and most frequently occurs in the long bones of young children or the vertebrae of patients at any age.¹⁰⁻¹² The higher incidence in the long bones of children due to the blood supply at the diaphysis, metaphysis and epiphyses which changes with age.¹³ Osteomyelitis may also occur in bones complicated by other conditions such as fractures following trauma, post-surgical intervention, diabetic foot infections or in fractures with implanted prosthesis resulting in non-healing fracture. The natural progression of osteomyelitis itself may result in osteomyelitis in a complicated bone. In osteomyelitis, the oedema or pus lifts the periosteum off the bone stimulating the formation of new bone known as involucrum and resulting in the death of the old bone (sequestrum) due to its blood supply being cut off resulting in dead bone within bone.¹³ The diagnosis of osteomyelitis may be daunting because surgery or trauma produce signs of inflammation like the inflammation which may mimic osteomyelitis and differentiating infection from inflammation becomes

crucial. Again, in some cases of osteomyelitis there may be hardly any local signs of inflammation making the diagnosis difficult.

The diagnosis of osteomyelitis

The diagnosis of osteomyelitis, as any clinical condition, depends on history, clinical symptoms, the evaluation of laboratory and medical imaging.^{4,14} In the case of osteomyelitis, there may be a known history of injury or intervention to the bone, previous osteomyelitis treatment or long-standing diabetes with. The definitive diagnosis of osteomyelitis is the culture of infective organisms on culture from a bone biopsy, marrow aspirate or the histological evaluation of a bone biopsy.¹⁵ However, a bone biopsy may not always be done especially when surgical intervention is not anticipated in the management of the infection. There are some clinical findings that may favour a diagnosis osteomyelitis.¹⁶ Any exposed bone or metallic implant or from a wound is clinically considered to be osteomyelitis as the bones are sterile in their usual anatomical site. A diabetic patient with bone fragments being discharged from an infected foot ulcer or discharging pus at the site of a patient previously treated for osteomyelitis or intramedullary pus present at surgery are clinical features that indicate the presence of osteomyelitis. In other cases, the diagnosis of osteomyelitis may be more difficult, and a combination of clinical, laboratory and imaging may be needed to arrive at the correct diagnosis. For example, if a patient with a prosthetic hip develops pain this could be due to infection or aseptic loosening. The differentiation of infected prosthetic joint from aseptic loosening may be challenging especially in low grade infections. The distinction between aseptic loosening and infection is crucial as the management of these two clinical entities is completely different.¹⁷ In most cases osteomyelitis in complicated bone there is no one test or imaging modality that can always correctly diagnose the infection. A combination of clinical features laboratory findings and imaging usually help in the diagnosis of osteomyelitis in complicated bone.¹⁸

The role of laboratory makers

Inflammatory markers such as the erythrocyte sedimentation rate, C-reactive protein, procalcitonin, white blood cell count may all help in the diagnosis and follow up of osteomyelitis¹⁹ These inflammatory markers are not only elevated in infection but also in aseptic inflammation. The role of these markers in osteomyelitis has been evaluated. In low-grade chronic infections of some complicated osteomyelitis some serum inflammatory markers have been shown to have an increased likelihood of infection being present. The markers of inflammation may be normal in some indolent microorganisms. Some inflammatory markers have shown the potential to monitor osteomyelitis in complicated bone.²⁰

Imaging in complicated osteomyelitis

Plain radiographs are the most utilized imaging modality in the initial evaluation of bone pathology. In suspected osteomyelitis, radiographs are usually the first modality used as they are readily available, easy to perform and inexpensive.²¹ The findings on plain radiographs for osteomyelitis may not be present for at least a week after an infection which may affect early diagnosis. On radiographs, osteopenia, periosteal reaction, cortical loss, endosteal scalloping and sclerosis are some radiographic features of osteomyelitis, but these findings are also present in other pathology and are not specific to infection. In many cases of osteomyelitis, plain radiographs may be insufficient to detect infection or determine the extent of infection particularly the soft tissue involvement and other imaging modalities are needed.²¹ Computer tomography (CT) scan has better at defining bone edges and identifying sequestrum and involucrum, however, in many cases of osteomyelitis the diagnostic accuracy is not satisfactory to be used alone in the clinical setting.^{21,22} Ultrasound has a limited role in assessing bone in osteomyelitis but can assess soft tissue and joints adjacent to bone and the joints where it may reveal subperiosteal collections or synovial fluid effusions.²¹ Magnetic resonance imaging (MRI) is often used in osteomyelitis and in many cases recommended as the imaging modality of choice.^{21,22} MRI provides excellent soft tissue resolution and can tell the extent of soft tissue involvement and can also detect early changes in bone marrow oedema of osteomyelitis.^{20,22} However, MRI may be inconclusive in some infections, or patient may have metallic insertion that prevent the use of MRI.^{23,24} Nuclear Medicine studies particularly FDG PET/CT play an important role when osteomyelitis is strongly suspected, and MRI is negative, inconclusive or contraindicated.^{25,26} Different nuclear medicine procedures have been used in the evaluation of chronic osteomyelitis. The SPECT bone scan although sensitive is non-specific and thus it is not useful in complicated osteomyelitis²⁶⁻²⁸. A negative three phase bone scan essentially excludes osteomyelitis due to its high negative predictive value. In complicated bone specificity as low as 10% is reported.²⁷ Ga-67 SPECT/CT was used in the past having better specificity and accuracy than three phase bone scan, however imaging requires different tracer and multiple imaging time and an expensive cyclotron produced SPECT tracer its role has been superseded by FDG PET/CT.^{27,28} In nuclear medicine, hybrid labelled white blood cell (WBC) SPECT imaging is often considered the gold standard for infection imaging.^{29,30} Hybrid imaging and better interpretation criteria the use of early and late combined with hybrid imaging have improved the accuracy of WBC imaging. WBC involves the direct handling of blood which is laborious and expensive and the delayed imaging after 20 hours after the injections means the results are only available after 24 hours.³⁰ FDG PET/CT has been demonstrated to be used as a useful imaging modality in the management of osteomyelitis especially in complicated bone. Understanding the advantages and limitations of FDG PET/CT in osteomyelitis of complicated bone is important in the to help in the diagnosis and management of osteomyelitis.

FDG PET/CT in osteomyelitis

There is increased glucose uptake by activated white blood cells including neutrophils, macrophages and lymphocytes in infections. [18F]Fluorodeoxyglucose (FDG) is a glucose analogue labelled with fluorine-18. FDG is taken up by the glucose transporters on the cell membrane of the immune cells. The intracellular FDG however remains trapped in the cell as it cannot be further metabolized after being phosphorylated. The phosphorylated FDG accumulates in the immune cells that have accumulated in the site of infected bone. The fluorine-18 positron emission tomography (PET) label emits positrons which undergo annihilation to yield photons which are detected by a PET camera.³¹ The PET camera is integrated with computer tomography (CT) which allows attenuation correction and anatomical localization of the PET data. Increased FDG is not limited to infection but other conditions like inflammation and malignancy. The uptake by noninfective conditions affects the interpretation of FDG PET/CT in osteomyelitis. FDG PET/CT has been used in the evaluation of different scenarios of chronic osteomyelitis. In a large systemic review of FDG PET/CT in osteomyelitis Llewellyn et al. evaluated 656 patients from 16 studies and found a sensitivity of 85% and specificity of 93%.³² However, being a heterogeneous condition and different sensitivities and specificities have been reported from meta-analysis and systemic analysis for the use of FDGPET/CT in the different osteomyelitis types.

Infected joint prosthesis

The European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) jointly released the second version of the guidelines for the use of FDG PET/CT in infection and inflammation.³³ Again, the appropriate criteria for the use of Nuclear Medicine imaging in musculoskeletal imaging was also published.³⁴ The number of joint prosthesis replacements is increasing exponentially as life expectancy increases.³⁵ The rate of infection after initial joint replacement is between 2%-2.4% but can rise to as high as 20% if revision of the implant is required.^{36,37} The management of infected joint prosthesis has great financial and clinical cost for health care system and individual.^{38,39} Periprosthetic joint infections are challenging to diagnose as it is usually a low-grade infection with nonspecific symptoms.^{40,41} The patient usually presents with pain in the affected area with very little erythema. The formation of biofilm by the causative pathogens on the surface of the implant further complicates the management as it helps the pathogens to evade the immune system and antibiotics.^{6,7} The hip and knee remain the most common sites of prosthetic joints implants although a small proportion involve other joints such as the shoulder. Previous comparisons of management across centres had been difficult because of a lack of definitions but this was addressed the last few years.⁴² Patients frequently present with pain in the affected area with fever and erythema occurring less

frequently. In cases where the diagnosis is challenging imaging can provide useful information. It is important to choose the appropriate imaging modality.³⁴

FDG PET/CT in infected prosthetic infection

The indications for FDG PET/CT use as per the recently revised joint EANM/SNMMI guidelines for infection and inflammation are patients with suspected prosthetic hip infections that require a test with high sensitivity preferable two years after the hip replacement and to rule out prosthetic joint infection when there is low suspicion of infection such as before a revision surgery.³³ There is currently lack of sufficient evidence for using FDG PET/CT in the prosthetic joint infections in knees and joints other than the hip according to the recent joint EANM/SNMMI guideline. Large systemic reviews and meta-analysis of the use of FDG PET/CT in periprosthetic infections reported sensitivity between 69%-88% and specificity 84%-96%.⁴³⁻⁴⁷ Vebrane et al, analysed 176 patients with knee prosthesis from 5 studies and found a sensitivity of 70% and a specificity of 84% in detecting infection.⁴³ The same group, Vebrane et al evaluated hip prosthesis in 725 patients from 12 studies and found a sensitivity of 69% and a specificity of 96%.⁴⁶ The most recent and largest meta-analysis till date by Hu et al., they evaluated 1437 patients from 23 studies and found a sensitivity of 85% and a specificity of 86%.⁴⁴ The joint EAN/SNMMI guidance suggest imaging can be limited to the field of view if no bacteraemia or sepsis is present.³³ The date and time from the revision must be considered when interpreting images. The absence of FDG uptake around the prosthesis can essentially exclude an infection. Different criteria have been suggested for prosthesis with different degree of success.^{48,49} The interpretation of infection in infected joint prosthesis is based on the pattern of uptake and location of FDG uptake rather than the intensity but different interpretation criteria have been proposed.^{34,43} For hip prosthesis FDG uptake in the middle of the femoral component is highly diagnostic with a sensitivity of 81% and specificity of 84%.⁴⁹ The presence of a sinus tract indicates infection. The presence of extensive and heterogeneous uptake in fluid within the muscle has also been considered as a sign of infection. It is important to note that FDG uptake not related to infection is often present reducing the specificity of FDG PET/CT in periprosthetic infections. FDG uptake not related to infection may be due to recent infection, peri-prosthetic inflammation, foreign body reaction, aseptic loosening. Metal related disease, fracture, pseudotumor and malignancy. The corresponding CT finding may also help detect the presence of infection. If there is fluid collection in soft tissue around the joint such as in fat or muscle surrounding a prosthesis they support the presence of infection but are not diagnostic in themselves. New periosteal bone is a specific finding for infection. The absence of joint distension makes infection very unlikely and bone lucency surrounding a prosthesis is nonspecific unless it is severe.⁵⁰ More research is needed to define the best time that FDG PET/CT after a prosthesis give the best yield of an infected prosthesis, the variability of the uptake depending on whether a cemented or non-cemented prosthesis was used and to

validate the different interpretation criteria that define infection. In other prosthetic joint infections, the role of FDG PET/CT was not recommended as it has not been by the recent joint EANM/SNMMI guidance in the different interpretation criteria require large multi-centred prospective study.³³ The interpretation criteria that is used for other joint prosthesis is the presence of FDG uptake in the interface between the prosthesis and the soft tissue, the presence of peri-prosthetic fluid collection with fluid uptake, however all these are may also occur in non-infective conditions and further studies are required.⁴¹

Fracture related infections

Infection may occur in bones that have been previous manipulated either by trauma or surgery. Persisted pain in bones that have previously been manipulated may be because of infection, inflammation or healing.³³ Fracture-related infections are debilitating, expensive and may result in permanent functional loss. It occurs in about 1.8% of closed fractures and up to 27% of open fractures.⁵¹ While the infections causing non-union of fractures range from acute to chronic some can be low-grade. Low-grade infections often lack clinical sign and are difficult to diagnose. Anatomical imaging is usually limited because of the previous bone violation and nuclear imaging studies have been found useful in these scenarios. As in the case of prosthetic joint infection, recent consensus in definitions of fracture-related infection have been published.⁵² Labelled white blood cell hybrid SPECT imaging has reported sensitivity of 79%-100% and specificity of 89%-97%.⁵³

FDG PET/CT in fracture related infections

The indications for FDG PET/CT in fracture-related infections are suspected fracture-related infections with or without metallic hardware and sternal wound infections. The role of FDGPET/CT is to distinguish infection from inflammation due to the previous trauma or intervention, to determine the extent of infection, to guide the planning and execution of surgical management if required, and to determine if infection has spread to other sites.³³ The patterns of uptake include focal and or heterogeneous uptake at the fracture site extending to the bone. In the presence of metallic implant there will be focal uptake involving the interface between the implant and the bone.³³ In the absence of infection FDG uptake is usually confined to the fracture line and it the FDG normalizes within 3 months.⁵⁴ Govaert et al. evaluated the role of FDG PET/CT in fracture related infections by a systemic review of the literature and found sensitivity from 86-94% and specificity from 76%-100%.⁵³ In a meta-analysis of FDG PET/CT in fracture related infections, that analysed 6 studies Zhang et al found a sensitivity of 89% and a specificity of 78%.⁵⁵

Sternal wound osteomyelitis

Sternal osteomyelitis is a very serious complication that may occur after surgery to the sternum. Sternal wound infection may occur in 1%-5% of cases after median sternotomy. The sternal infection may lead to multiple organ failure or death, Mortality rates of 10%-30% have been reported for sternal wound infections.⁵⁶ The high morbidity and mortality makes early diagnosis and management paramount. The bone has been altered by surgery and anatomical imaging is less than optimal. Nuclear imaging studies may address this condition.³⁴

FDG PET/CT in sternal osteomyelitis

FDG PET/CT was noted to have a sensitivity of 91%-98% and a specificity of 93% to 97% in the evaluation of sternal osteomyelitis.^{57,58} It was noted that FDG PET/CT outperformed CT and could localize the infection and provide an infection 'map' that allowed treatment of infection. FDG PET/CT was also useful in monitoring the sternal wound infection after debridement.⁵⁸ A notable but expected drawback was the relative diminished sensitivity when the FDG PET/CT was conducted very soon after the surgery.⁵⁸ After sternotomy FDG uptake in FDG can persists for several years.⁵⁷

Special consideration FDG PET/CT in complicated osteomyelitis

The preparation of patients for infection imaging follows the general guidance of performance of PET/CT in oncology but there are few modifications specific to infection imaging.³³ While hyperglycaemia was not found to affect FDG PET/CT detection of infection another study showed that the yield of FDG PET/CT in detecting infection in bacteraemia decreased as the glucose increased.^{59,60} In patients with poorly controlled diabetes all efforts must be made to bring the glucose levels to as low as possible. In patients where bacteraemia or sepsis is not suspected the field of view can be limited to the site of infection. When the source of infection is under investigation cardiac suppression protocols which are used in FDG evaluation of endocarditis must be used (Figure 1, 2, 3).⁶¹

Conclusion

FDG PET/CT is an important imaging modality in imaging osteomyelitis of complicated bones. Although there are many questions that require validation or clarification with large prospective studies. FDG PET/CT can be used in different forms of osteomyelitis and may even be the imaging of choice in some indication. FDG PET/CT is a good alternative in imaging osteomyelitis when MRI is contraindicated.

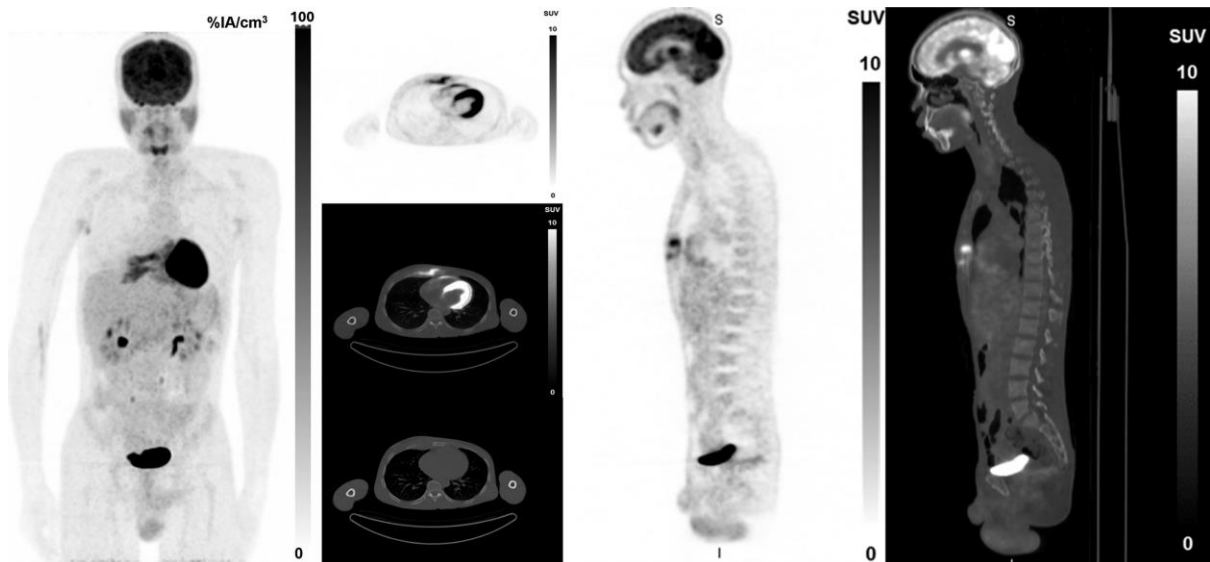


Figure 1.—37-year-old male with a history of persistent para-sternal abscess not resolving on antibiotics and surgical debridement. Suspected sternal osteomyelitis. 7mCi F-18 FDG given followed by whole body PET/CT after 60-minutes. Shown are MIP image (A), axial (B) PET only, PET/CT and CT; sagittal PET only and PET/CT (C and D, respectively). Metabolically active expansile soft-tissue mass with encasement and destruction of the distal 4th and 5th ribs at the costochondral junction. CT component: irregularity of the 6th right sternal border-sternal infiltration not convincing. FDG PET: metabolic active noted in the lower sternum, confirmatory of sternal involvement. This case demonstrates the superiority of FDG in evaluating osteomyelitis, although this is not convincing on CT due to the absence of destructive bone lesions, FDGPET demonstrates metabolic activity suggestive of an infective-inflammatory process

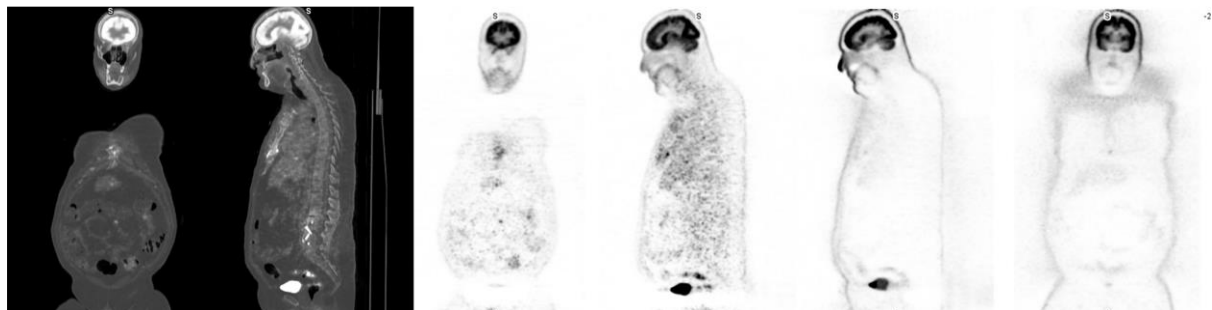


Figure 2.—49-year-old male with a history of CABG complicated by sepsis- surgical debridement done 6-months ago, with suspected osteomyelitis. 14mCi FDG followed by whole body PET/CT after 60-minutes. Corrected PET and PET/CT images (A-D) show diffusely increased metabolic activity in the sternum. At first glance this would be suspected related to inflammation with or without infection involving the sternum. Uncorrected PET only images (E and F sagittal and coronal images respectively) a focus of increased uptake is seen in the lower retrosternal region ruling out sternal osteomyelitis Further review shows that the rest of the sternal uptake is related to attenuation correction artefact related to the sternotomy wires.

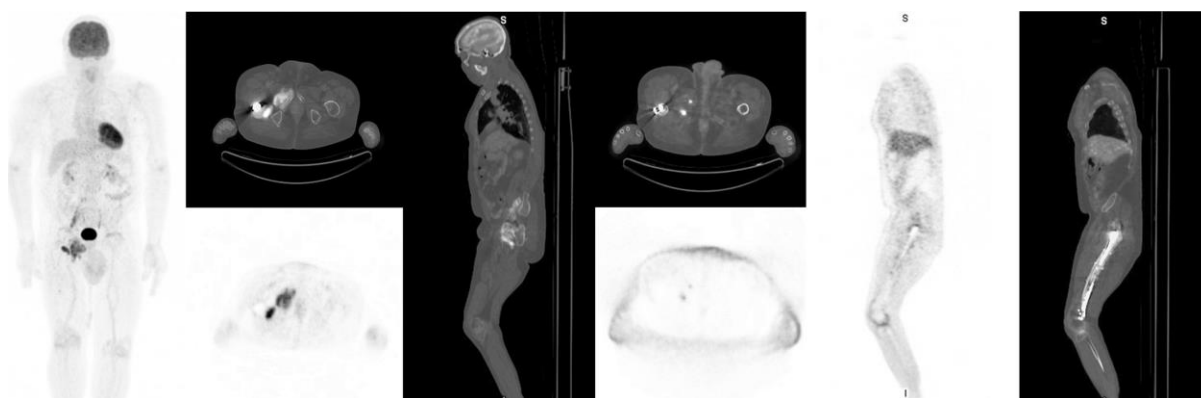


Figure 3.—63-year-old male with previous right hip replacement 20-years ago. Right peri-prosthetic fracture, complicated by non-union 13-years ago. Last revision 7-years ago. Concern that is sepsis is the underlying cause of non-union. WBC study showed no evidence of sepsis in the right hip. 10mCi FDG then PET/CT after 60-minutes. MIP (A) shows two areas of diffusely increased uptake in the right hip. Seen on PET/CT images (B-D) this localizes areas to heterotrophic calcification lateral to the superior and inferior pubic ramus, pubis, anterior column of the acetabulum as well as medial to shaft of the femur (SUVmax: 13.54). No significant uptake noted in mid-femoral shaft in the site of non-union (E-H). FDG uptake in HO, suggestive of active inflammation, is known as a pitfall of 18 F-FDGPET/CT imaging for an infective process. CT component: irregularity of the 6th right sternal border-sternal infiltration not convincing. FDG PET: metabolic active noted in the lower sternum, confirmatory of sternal involvement. This case demonstrates the superiority of FDG in evaluating osteomyelitis, although this is not convincing on CT due to the absence of destructive bone lesions, FDG PET demonstrates metabolic activity suggestive of an infective-inflammatory process.

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